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ARTICLE

Neurobehavioral Deficits in Offspring of Schizophrenic Parents: Liability Indicators and Predictors of Illness

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High-risk research in schizophrenia incorporates several different strategies for studying individuals who are defined by different criteria as being at risk for future development of schizophrenia. Variables from a wide range of domains have been included in these studies. Several reviews of high-risk research have attempted to cover the field broadly, whereas others have been more sharply focused on research subjects defined by specific criteria or on particular classes of variables. Among the review articles and collections of project reports on high-risk research in the past two decades are: Watt et al. [1984: Children at risk for schizophrenia: a longitudinal perspective]; Nuechterlein and Dawson [1984: Schizophr Bull 10:160–203]; Nuechterlein [1986: J Child Psychol Psychiatr 27:133–144]; Erlenmeyer-Kimling and Cornblatt [1987: J Psychiatr Res 26:405–426]; Goldstein and Tuma [1987: Schizophr Bull 13:369–371]; Asarnow [1988: Schizophr Bull 14:613–631]; Moldin and Erlenmeyer-Kimling [1994: Schizophr Bull 20:25–29]; Mirsky [1995: Schizophr Bull 21:179–182]; Gooding and Iacono [1995: Manual of developmental psychopathology] McNeil [1995: Epidemiol Rev 17:107–112] Olin and Mednick [1996: Schizophr Bull 22:223–240]; Cornblatt and Obuchowski [1997: Intl Rev Psychiatry 9:437–447]. This paper presents an overview of findings from recent (the past decade and a half) prospective studies of children of schizophrenic parents, with a focus on neurobehavioral (neurocognitive, neuromotor, and neurophysiological) variables that may reflect aspects of the genetic liability to schizophrenia and related disorders. The few neuroimaging studies on children of schizophrenic parents are also briefly mentioned. Because of space limitations, the overview is not intended as a comprehensive or detailed review of this area of high-risk research. Am. J. Med. Genet. (Semin. Med. Genet.) 97:65–71, 2000. **2000 Wiley-Liss, Inc.**

KEY WORDS: high-risk research; offspring of schizophrenic parents; neurobehavioral deficits; genetic liability indicators

INTRODUCTION

High-risk research in schizophrenia started in the 1950s and early 1960s, when genetic hypotheses about psychiatric disorders had yet to rebound from a long period of neglect. The initial aims were twofold: (1) to describe early life-circumstances of individuals at increased risk for schizophrenia and (2) to identify neurobehavioral or other trait deficits that might predict later development of the disorder. Subsequently, acceptance of schizophrenia as a complex, multifactorial disorder led to further goals: (3) clarification of possible interactions between genetic and environmental factors and (4) evaluation of premorbid dysfunctions as phenotypic indicators of schizophrenia-susceptibility genes.

This paper presents an overview of findings over the past two decades in prospective studies of children of schizophrenic parents.

Initial high-risk studies [Mednick and Schulsinger, 1968; Fish, 1984], and many of those that came after, entailed prospective follow-up of offspring of schizophrenic parents (OSPs), whose life expectancy rates for schizophrenia had been shown in older family morbidity-risk studies [Gottesman et al., 1987] to be between 10% and 15%, compared with a 1% general population risk. Later study designs have used: (1) prospective follow-up of adolescent or young adult subjects selected for traits hypothesized to characterize preschizophrenic individuals, (2) follow-back of archival materials collected at younger ages on schizophrenic patients drawn from large population-based cohorts or other registry samples, or (3) neurobiological testing of adult nonpsychotic relatives of schizophrenic probands. The three later approaches can address some of the goals of high-risk research mentioned above but, unlike prospective studies of OSPs, cannot address all of them. Follow-up or follow-back studies based on other grounds than genetic relationships may provide information about early precursors and suggest predictors of later illness, but these approaches do not address questions about genetic factors. Testing of the adult relatives potentially yields infor-

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mation about nonclinical indicators of the genetic liability, but does not provide information about early environmental or other factors as precursors of schizophrenia.

Early life circumstances frequently hypothesized to be risk-increasing precursors include prenatal and labor-delivery complications, specific classes of environmental stressors or excessive accumulation of nonspecific stressors, and certain aspects of the family environment associated with characteristics of the parents (e.g., deviant communication or child rearing patterns)—although information about family environments of OSPs may not be generalizable, given that only 10–15% of schizophrenic patients have an affected parent. Some of these factors, formerly conceptualized strictly as *environmental* precursors, are now seen to involve gene-environment interaction. For example, a recent study of adopted-away OSPs and controls showed development of psychiatric disorders in OSPs reared in disturbed adoptive homes but not in those with good adoptive homes or in controls reared in disturbed homes [Wahlberg et al., 1997]. An earlier [Wender et al., 1974] cross-fostering study, comparing children of schizophrenic biological parents reared by normal adoptive parents and children of normal biological parents reared by adoptive parents who later became schizophrenic, also suggested gene-environment interaction, in that the genetically high-risk OSPs reared in healthy homes showed higher rates of schizophrenia spectrum disorders than the genetically low-risk children reared in disturbed homes (by schizophrenic parents).

Early neurobehavioral and other (e.g., social) trait deficits have been sought in at-risk groups as possible predictors of future schizophrenia, on the assumption that processes basic to the illness appear long before clinical signs. This assumption was a forerunner of the current neurodevelopmental hypothesis [Weinberger, 1986; Murray and Lewis, 1988], that suggests that, probably in interaction with a genetic liability, pre- or perinatal insults to the developing brain lead to neurobehavioral dysfunctions early in childhood or infancy in preschizophrenic individuals. From the start of high-risk research, these trait deficits were expected to elucidate the pathophysiology of the illness and to suggest the focus for future preventive intervention strategies.

In recent years, many investigators have attempted to equate the search for predictors with the search for indicators of genetic liability to schizophrenia. Not all good predictors are liability indicators or vice versa, however. For example, deficits in adolescent social or school behavior, sometimes reported to be associated with later schizophrenia spectrum disorders, are more apt to be early prodromal signs or reflections of independent, genetically-influenced traits that may act as potentiators of the illness in individuals with the schizophrenia genotype [Meehl, 1962], than to reflect schizophrenia-susceptibility genes per se. On the other hand, some presumed liability-indicator traits may occur so frequently in at-risk individuals who remain free of future illness that they do not have good overall accuracy as predictors. Predictors must meet the same criteria required to qualify a trait as a liability indicator [e.g., Erlenmyer-Kimling and Cornblatt, 1987; Hans et al., 1999] but must also be identifiable sufficiently early to be distinguishable from prodromal signs and must be strongly associated with later development of schizophrenia-related disorders.

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Although schizophrenia was originally considered *the* outcome of importance, recent interest has also been directed to several other common outcomes in genetic-risk subjects, ranging on a severity spectrum from mild signs to personality disorders almost as disabling as schizophrenia itself. In addition to a substantial proportion of OSPs predicted (according to any genetic hypotheses) *not* to develop any signs of the illness because they do not have the genetic liability, other OSPs who do carry susceptibility genes may remain free of the illness—as do 50% of the MZ cotwins of affected twins [Gottesman and Bertelsen, 1989].

High-risk researchers have attempted to validate trait deficits as predictors of some type of disturbance related to schizophrenia, by looking at the longitudinal association between variables examined at younger ages and later emergence of several types of disturbance, including general level of adjustment/maladjustment, positive/negative symptoms, and the cluster of diagnostically-defined personality disorders (chiefly schizotypal and paranoid personality disorders) that are often, but are not always, considered to be specific to the genetic liability to schizophrenia, as opposed to other psychiatric disorders.

STUDIES OF OSPs

Diagnostic Outcomes

Diagnostic evaluations in adulthood or late adolescence have been completed or are being conducted currently in six prospective studies of OSPs. These studies, with numbers and ages of the subjects at the start, ages at the final diagnostic assessments, and prevalence rates of schizophrenia-related psychoses are listed in Table I. As shown, all studies included normal control subjects in addition to the OSPs, and some included psychiatric controls as well. The NYHRP included offspring of parents diagnosed with major affective disorders, whereas the SHRS and JIDS included offspring of parents (mothers only in the SHRS) with several types of types of nonschizophrenic disorders.

Although many subjects in these studies had not passed through the maximum risk period for developing schizophrenia at latest assessment, the studies agree in showing higher prevalence rates (uncorrected for age) for schizophrenia and related psychoses (mainly schizophrenic schizoaffective disorder, unspecified or atypical psychoses, other schizophrenic psychoses)

TABLE I. Prospective Studies of Offspring of Schizophrenic Parents With Neurobehavioral Assessments and Follow-Up to Adulthood

Characteristics of the Studies									
Study name (abbreviation)	New York Infant Study (NYIS)	Copenhagen High-Risk Project (CHRP)	Israeli High-Risk Study (IHRS)		New York High-Risk Project (NYHRP)		Swedish High-Risk Study (SHRS)	Jerusalem Infant Development Study (JIDS)	
Location	New York City	Denmark	Israel		New York State		Sweden	Jerusalem (Israel)	
Principal investigator[a]	B. Fish	S. Mednick	A. Mirsky		L. Erlenmeyer-Kimling		T. McNeil	J. Marcus	
Year started	1952	1962	1967		Sample A: 1971 Sample B: 1978		1973	Targets: 1973 Sibs ≃1983	
Subject information									
Age at start of study (years)	Birth	9–20 m = 15.1	8–15 m = 11		7–12 m = 9.0–9.5		Prenatal	Targets: birth Sibs: 8–13	
					A	B			
Age at last diagnostic assessment (years)	20–26 (26–27 partial sample)	m = 39–42	21–27 m = 30		m = 32.6	m = 27.1	23 (ongoing)	14–21 m = 17.5	
N[b]								Target	Sibs
Schizophrenia risk	12	207	50	½ kibbutz reared	63	46	16	19	10
Other psychiatric risk	—	—	—		43	39	58	20	11
Normal controls	12	104	50	½ town reared	100	65	100	19	7
Prevalence of schizophrenia-related psychoses[c]									
Schizophrenia risk	8.5%	20.8%	8.0%		18.5%	7.7%	—	4.1%	Targets and sibs
Normal controls	0.0%	2.9%	0.0%		1.1%	0.0%	—	0.0%	

Assessments ongoing

[a]Other first authors referenced in this review: CHRP, J. Parnas, T. D. Cannon; IHRS, S. Hans, L. Ingraham, J. Marcus; NYHRP, B. Cornblatt, R. Dworkin, L. Freedman, D. Friedman, S. Ott, D. Rosenberg, E. Squires-Wheeler; SHRS, E. Schubert; JIDS, S. Hans.
[b]Ns as start of study.
[c]Prevalence rates (uncorrected for age) for schizophrenia-related psychoses: schizoaffective disorder, other schizophreniform psychoses, and unspecified (atypical) psychosis.

in the OSPs than in normal control and psychiatric control offspring. Rates of these disorders in the OSPs range from 7.7% (NYHRP, Sample B) to 20.8% (CHRP) and in the normal controls, from 0% to 2.9%, in the four studies with assessments in the mid-twenties or older (Table I). In the NYHRP, the sole study with follow-up into mid-adulthood that included psychiatric controls, none of the subjects in this control group in either sample developed schizophrenia per se, although 9.8% in Sample A (but 0% in Sample B) received diagnoses of schizoaffective disorder, mainly schizophrenia. The rates of schizophrenia in the four studies with adulthood follow-up are not significantly different from the average morbidity risk among OSPs in the older family study literature [Gottesman et al., 1987].

Prevalence rates for the Cluster A personality disorders vary more widely, ranging from 0% in the IHRS [Ingraham et al., 1995] to 50% in the NYIS [Fish, 1984]. Rates of affective disorders in the OSPs seem high in the IHRS [Ingraham et al., 1995] and NYHRP [Erlenmeyer-Kimling et al., 1995] but

are similar to those for the normal controls in each of these studies. Thus, on the whole, the clinical outcomes in the OPSs followed in the prospective studies are in accord with expectations.

Neurological/Neuromotor Dysfunctions

Interest in neurological and motor dysfunctions in OSPs stemmed, in part, from Meehl's [1962] concept of a neurointegrative deficit expressed from very young ages in preschizophrenic individuals and, in part, from Fish's [1984] observation in the NYIS (the earliest high-risk study) of a pattern of developmental dysregulation in neuromotor functions in about half of the OSPs in infancy and young childhood. Subsequently, deviant neurological and motor functioning have been reported in OSPs, compared with controls, in infancy and mid-childhood in the SHRS [McNeil et al., 1993] and JIDS [Marcus et al., 1987] and in mid-childhood in the IHRS [Marcus et al., 1987] and the NYHRP [Erlenmeyer-Kimling and Cornblatt, 1987]. Motor incoordination was the most common childhood neuromotor deviation. There are some inconsistencies, however: for example, the SHRS did not find stability between the infant and childhood assessments [McNeil et al., 1993] or a relationship with obstetric complications [Schubert et al., 1996], whereas the JIDS reported both stability and a relationship with obstetric complications [Hans et al., 1999].

Dysfunctions in neurological and neuromotor functioning have been proposed as liability-indicators [e.g., Hans et al., 1999] and growing evidence suggests that they may be good predictors of schizophrenia-related conditions in OSPs. Neurological dysregulation in infancy was associated with schizophrenia spectrum disorders in all of the OSPs who developed such disorders in the NYIS [Fish, 1984], and performance on a neurobehavioral battery with a large motor component was associated with concurrent spectrum disorders in adolescence in the JIDS [Hans et al., 1999]. In the NYHRP, childhood neuromotor dysfunctions predicted affective flattening in adolescence [Dworkin et al., 1993] and identified 75% of the OSPs who developed adulthood schizophrenia-related psychoses [Erlenmeyer-Kimling et al., submitted]. Moreover, schizophrenic patients in a follow-back study were distinguished from their normal siblings based on childhood neuromotor disturbances seen in home movies [Walker et al., 1994].

Neurocognitive Functions

Cognitive deficits of several types have been reported in OSPs, compared with controls, in most of the studies listed above, as well as in several other studies of OSPs without completed longitudinal follow-up [Nuechterlein, 1983; Schreiber et al., 1992]. Consistent findings have been obtained especially for measures of attention in tasks with high-processing demands [Nuechterlein, 1983; Cornblatt and Erlenmeyer-Kimling, 1985]. In the NYHRP, a summary measure of performance on several attentional tests given in mid-childhood [Erlenmeyer-Kimling and Cornblatt, 1992] showed impairment in about 25% of the OSPs in both independent samples, compared with under 10% of subjects in the affective-risk and normal control groups. The attentional index, shown to be heritable and stable over time [Cornblatt et al., 1989], was associated, in OSPs, but not controls, with poor social competence [Dworkin et al., 1993], poor global adjustment [Erlenmeyer-Kimling and Cornblatt, 1987], and anhedonia [Freedman et al., 1998] in adolescence and with early adulthood social deficits [Cornblatt et al., 1992; Freedman et al., 1998]. The attentional index predicted 58% of the subjects who developed schizophrenia-related psychoses by mid-adulthood [Erlenmeyer-Kimling et al., submitted].

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Poor performance on memory tasks, especially those involving distraction conditions, has also been reported in OSPs in several studies [Nuechterlein, 1986; Erlenmeyer-Kimling and Cornblatt, 1987]. In the NYHRP, verbal short-term memory assessed by the WISC digit-span task administered in childhood, was significantly related both to amplitude decrements in the P3 component of event-related potentials in adolescence and to negative symptoms in adulthood in the OSPs, but not the other risk groups [Squires-Wheeler et al., 1997]. (Memory and P3 amplitude were unrelated to positive symptoms.) A verbal short-term memory factor consisting of the same childhood digit-span task and a complex attention-span task predicted 83% of the NYHRP OSPs who developed adulthood schizophrenia-related psychoses and showed high specificity to these psychoses, compared with other psychiatric outcomes, and to OSPS, compared with the other risk groups [Erlenmeyer-Kimling et al., submitted].

A number of other cognitive functions, including general IQ tests and their subtests, have been investigated in prospective studies of OSPs [Nuechterlein, 1986; Erlenmeyer-Kimling and Cornblatt, 1987]. Lower IQs, sometimes reported in schizophrenic patients and OSPs compared with normal controls, probably reflect polygenic potentiators that are independent of schizophrenia-susceptibility genes [Meehl, 1962]. Patterns of subtest impairments and scatter that are specific to schizophrenia-risk, rather than risk for other disorders or no disorder [Ott et al., 1998], may well be relevant, however, to the genetic liability of schizophrenia.

Psychophysiology and Brain Imaging

Smooth-pursuit eye movement (SPEM) dysfunctions, reported in a number of studies [Levy et al., 1994] to occur in 50% or more of the unaffected relatives of schizophrenic probands have been assessed in OSPs in adulthood [Rosenberg et al., 1997], adolescence [Mather, 1985], and childhood [Ross et al., 1996]. The OSPs had greater SPEM

dysfunctions than normal control subjects and more frequent anticipatory saccades [Ross et al., 1996; Rosenberg et al., 1997]. The adult OSPs in the NYHRP had poorer SPEM than offspring of bipolar parents (who did not differ from normal controls) and a greater rate of anticipatory saccades than offspring of unipolar depressed parents [Rosenberg et al., 1997]. Thus, the small body of data from high-risk research, together with extensive data on unaffected first-degree relatives of schizophrenia probands, supports the claim that SPEM dysfunctions may be phenotypic indicators of the genetic liability to schizophrenia [Levy et al., 1994].

Psychophysiological examinations in prospective studies of OSPs have produced mixed results, both within and between studies. Several studies [Steinhauer and Friedman, 1995] failed to replicate a pattern of autonomic nervous system activity (electrodermal hyperresponsiveness) reported in the CHRP OSPs who later became ill [Mednick and Schulsinger, 1968]. Reanalyses of the CHRP data [Cannon et al., 1993], however, suggest that these OSPs showed two patterns, each leading to different symptoms, in interaction with different environmental factors: hyperresponsiveness with early unstable rearing was associated with positive symptoms and hyperresponsiveness with birth complications was associated with negative symptoms.

Event-related potential (ERP) components were initially reported in one sample [Schreiber et al., 1992] to show prolonged latencies and no amplitude reductions in OPSs, but at retesting these subjects had reduced P3 amplitude with no prolongation. OSPs in the NYHRP had no P3 or Slow Wave differences compared with normal controls or offspring of affectively ill parents, and no associations with childhood attentional measures, global adjustment in adolescence, or schizophrenia-related psychoses in adulthood [Friedman and Squires-Wheeler, 1994]. As noted earlier, however, P3 amplitude reduction was associated with poor global adjustment and negative symptoms in adulthood in all three risk-groups [Squires-Wheeler et al., 1997]. Deficits in sensory gating, measured by lack of attenuation in the P50 ERP component, have been reported for many adult relatives of schizophrenic probands but have not yet been studied in OSPs.

Four newly-started prospective studies include structural or functional brain imaging. (These are studies by Johnstone in Scotland, Keshavan in Pittsburgh, Sharma in the United Kingdom, and Tsuang in Boston.) Preliminary results from one of these studies using MRI and proton magnetic resonance spectroscopy (MRS) examinations in child and adolescent OSPs have been reported briefly by Keshavan et al. [1997]. The OSPs had reduced left amygdala volume, smaller overall brain volume, and enlargement of the third ventricles, consistent with other findings in schizophrenic families [e.g., Cannon et al., 1998], obligate carriers of schizophrenic patients [Sharma et al., 1997], and adult, already affected OSPs [Cannon et al., 1994]. Computed tomography (CT) scans were used in one of the older prospective studies (CHRP) to compare adult OSPs who had developed schizophrenia with those who had developed schizotypal personality disorder, nonspectrum psychiatric disorders, or no disorders [Cannon et al., 1994]. The subjects with schizophrenia and schizotypal personality disorder showed greater sulcal enlargement than OSPs with nonspectrum or no disorders or than normal controls with or without psychiatric disorders; however, ventricular enlargement was greater in the OSPs with schizophrenia compared with all of the other OSPs or normal controls. Moreover, the type and degree of CT abnormalities were reported to show interactions between degree of genetic risk (illness in one or both parents) and birth complications [Cannon et al., 1994].

SUMMARY

Prospective studies have identified dysfunctions in several neurobehavioral domains that are more prevalent in OSPs during childhood or adolescence than in normal controls and (when tested) control offspring of parents with other psychiatric disorders. In agreement with findings often presented for schizophrenic patients and their adult relatives [Moldin and Erlenmeyer-Kimling, 1994], high-risk research has consistently shown deficits in OSPs for neuromotor and cognitive—especially attentional and memory—functions, as well as in SPEM in the few studies examining that domain. Reports of psychophysiological dysfunctions or brain abnormalities in OSPs have been less consistent or not put to the test of replication.

Prediction to schizophrenia per se, the original goal of high-risk research, has been attempted in the CHRP and NYHRP. A broader range of schizophrenia-spectrum disorders has been used to evaluate the predictive value of childhood and adolescent neurobehavioral measures in many studies, which having started with small to moderate-sized samples and having not carried follow-up far into the schizophrenia-risk period, have identified very small numbers of subjects with schizophrenia thus far. Several measures do seem to be moderately good to excellent predictors of later spectrum disorders or particular symptom dimensions. Some of the outcome conditions themselves (e.g., classifications of schizotypal personality disorder or of positive/negative symptoms), however, may not be specifically related to schizophrenia compared with major affective disorders [e.g., Squires-Wheeler et al., 1988; Ingraham and Kety, 1989; Kety et al., 1994; Lyons et al., 1994], thus raising questions about the specificity of the neurobehavioral dysfunctions as well. Another problem for the validation of predictors is that

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subjects have sometimes been sufficiently old at testing to raise a concern that they may already have entered a prodromal phase; this, of course, could entangle antecedents and consequences of the illness.

The search for phenotypic indicators of the genetic liability to schizophrenia has been endorsed enthusiastically by many high-risk researchers. Indeed, it is popular to claim that a variable represents a "marker" if it gives evidence of greater dysfunction in OSPs than controls or seems to be associated in some way with putative spectrum conditions. Although the criteria required for liability indicators have usually not been taken into account, the claims advanced for neurobehavioral dysfunctions that consistently flag OSPs, preschizophrenic individuals, and relatives of schizophrenic patients across studies are probably valid. Some of the dysfunctions seen in neuromotor and cognitive traits, and in SPEM, in the prospective studies of OSPs are thus supported as probable liability indicators expressed at very young ages. Many other variables claimed as "markers," however, need to be tested for replicability across studies, stability over time, heritability, and specificity to schizophrenia.

Attempts to relate observed brain pathology to some of the traits claimed by high-risk researchers to be liability indicators do not extend to other dysfunctions seen in OSPs or in adult relatives of schizophrenic probands. Equally important, there have been no attempts from a genetic viewpoint to clarify commonalties among the several putative indicators by searching for quantitative trait loci (QTLs) that may underlie more than one of the traits. Thus, although high-risk studies have provided a great deal of information about at-risk subjects and have offered many clues about predictors and liability indicators, many claims remain to be substantiated and many questions about antecedents of schizophrenia remain to be clarified. Let the reader beware.

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